of inflammatory cytokine genes was also detected in the App^{NLGF}::-$Keap1^{KD}$ mutants. We then treated App^{NLGF} with 6-(Methylsulfinyl)hexyl isothiocyanate (6-MSITC), an activator of NRF2, in the drinking water for 11 months to analyze the effects of pharmacologically activated KEAP1-NRF2 system. 6-MSITC-treated App^{NLGF} mice also displayed reversed memory function and differential distribution of phagocytic cells compared to the vehicle-treated App^{NLGF} mice. **Conclusions:** These results suggest the activation of KEAP1-NRF2 system can mitigate AD-related phenotypes by regulating oxidative stress and inflammation.

P3-179 ABERRANT PERK ACTIVATION IS ASSOCIATED WITH THE DEPLETION OF NRF2 SIGNALING AND THE INCREASE OF OXIDATIVE BURDEN IN DS PATHOLOGY

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Background: The accumulation of misfolded proteins in the endoplasmic reticulum triggers a cellular stress response called the Unfolded Protein Response (UPR). Long-term activation of the UPR mediates neuronal dysfunction in Alzheimer disease (AD). In our previous project, we identified the potential contribution of the PERK-mediated disruption of protein synthesis in DS mouse models. However, no data on DS subjects have been collected so far. Our project aims: 1) to investigate the status of UPR in human brain from DS and DS/AD and in PBMCs from living DS children; to restore, in a mouse model of DS, the PERK pathway by using a well-established PERK inhibitor that could mitigate the early activation and result in reduced brain pathology. **Methods:** Human frontal cortex and PBMCs were used to investigate the UPR status during the development of DS and its potential involvement in the progression to AD. Further, the PERK inhibitor GSK2606414 has been tested in Ts2Cje (mouse model of DS), by intranasal delivery, to target directly the brain and rescuing the aberrantly activated PERK-arm of the UPR. The analysis of the proteins of interest has been carried out by immunofluorescence and Western Blot. **Results:** Our data demonstrated that the aberrant induction of UPR in the frontal cortex of DS patients, as indexed by the chronic hyperactivation of the PERK arm, was associated with the depletion of Nrf2-related antioxidant response in the early and in the late stage of the disease. Similar outcomes were observed in PBMCs from DS children supporting the link with DS pathology. The use of the GSK2606414 compounds in DS mice was able to recover PERK over-activation, rescue Nrf2 signal and reduce oxidative damage to proteins (protein-bound 3NT and HNE). Intriguingly, PERK inhibition led to positive outcomes in mice by a mechanism distinct from its canonical one. **Conclusions:** Our data provide novel insight into the physiological mechanisms of AD development in DS individuals and support that PERK plays an important role in mediating neuronal damage. These data also suggest the exploration of PERK inhibitors as therapeutic options in reducing AD-related cognitive decline in DS and normal population.

P3-180 ALTERED SYNAPTIC GLUTAMATE HOMEOSTASIS UNDERLIES SEIZURE-INDUCED COGNITIVE DECLINE IN YOUNG APP/PSEN1 MICE

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Background: Recent evidence has highlighted the co-occurrence of epilepsy with Alzheimer's disease as a significant contributor to cognitive decline. Minor epileptogenic events, such as absence seizures, and events occurring during sleep may go unidentified and therefore untreated in these patients. Epileptogenic signaling may result from alterations in synaptic glutamate homeostasis, which serves as a targetable mechanism underlying this potential source of cognitive decline at early stages of Alzheimer's disease. **Methods:** Young APP/PSEN1 and wild-type mice were treated with low doses ($\leq$10 mg/kg) of kainic acid, an agonist for the glutamatergic kainate receptor, twice per week for up to 8 weeks, beginning at 12-16 weeks of age. Low concentrations of kainic acid were used to avoid overt, observable seizures. Epileptogenic signaling was measured via a telemetry EEG system weekly for up to 6 weeks. Learning and memory were assessed using a battery of behavioral tasks including the Morris water maze to explore changes in hippocampal function. Possible deficits in synaptic transmission and plasticity were studied via tetanus-induced long term potentiation (LTP) in hippocampal slices from kainic acid treated wild-type and APP/PSEN1 mice. **Results:** APP/PSEN1 mice were more susceptible to the effects of kainic acid and showed greater numbers of altered epileptogenic signaling events in the absence of observable seizure behaviors. Even at low doses of kainic acid, APP/PSEN1 mice were also more likely to die in the days following administration. The surviving APP/PSEN1 mice showed memory impairments during reversal learning in the Morris water maze. Five days of administration of kainic acid disrupted markers for pre- and post-synaptic signaling in hippocampal slices in both wild-type and APP/PSEN1 mice, although the pattern of these effects differed according to genotype. **Conclusions:** Mild epileptogenic signaling events can impact cognitive decline in young APP/PSEN1 mice, prior to significant accumulation of beta-amyloid and likely reflect changes in glutamatergic signaling.

P3-181 TREATMENT WITH THE DIRECT THROMBIN INHIBITOR DABIGATRAN ETEXILATE REDUCES OXIDATIVE STRESS *IN VIVO* IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Background: The coagulation factor thrombin is a multifunctional serine protease that contributes to oxidative stress and inflammation. Thrombin has been shown to be neurotoxic and is elevated in the brain and cerebrovasculature in Alzheimer's disease (AD). We have identified thrombin as a key mediator of cerebrovascular activation in AD and have data demonstrating that thrombin inhibition diminishes vascular activation in an animal model of AD.